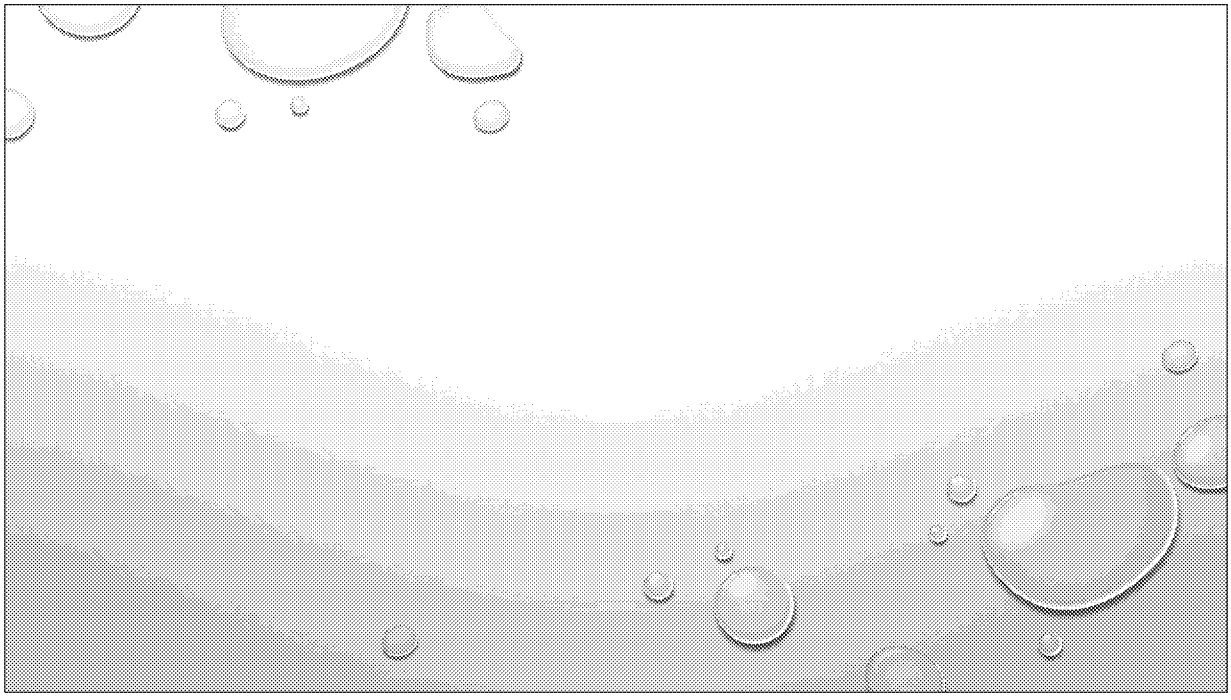


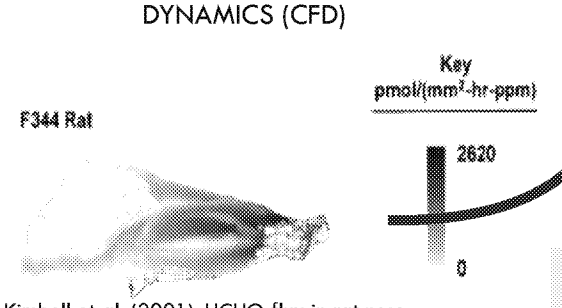
A BRIEF ANALYSIS OF THE (NASAL) DOSIMETRY OF INHALED FORMALDEHYDE

PAUL M. SCHLOSSER

The analysis shown and views expressed here are my own and do not necessarily reflect the views or policies of the U.S. EPA.

EARLY, "SIMPLE" MODEL STRUCTURE

COMPUTATIONAL FLUID DYNAMICS (CFD)



Kimbell et al. (2001), HCHO flux in rat nose

TISSUE COMPARTMENT (PBPK)

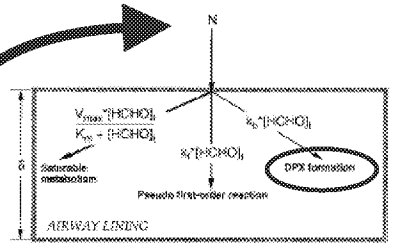


FIG. 2. Diagram showing nasal-lining compartment and HCHO pathway fluxes. [HCHO]$_t$, HCHO tissue concentration; N, HCHO mass flux into the nasal lining; δ, tissue thickness; V_{max}, K_m, k_2, k_1, kinetic constants for metabolism and elimination of HCHO. Relative importance of fluxes are indicated by the thickness of arrows.

Hubal et al. (1997); incorporated into Conolly et al. (2000) and later papers

CALIBRATION TO DNA-PROTEIN CROSSLINK (DPX) DATA

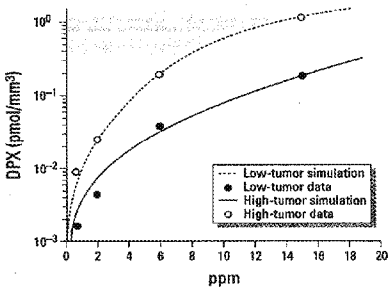
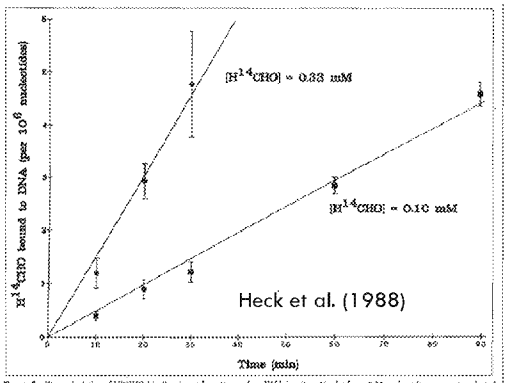


Figure 1. Simulation of F344 rat nasal mucosal DPX data obtained at the end of a 3-hr inhalation exposure to formaldehyde gas. The differences in the predictions of the low-tumor and high-tumor areas were obtained by site-specific tissue thickness and formaldehyde flux estimates.

Conolly et al. (2000)

KEY IN-VITRO CALIBRATION DATA



Heck et al. (1988)

BUT WHAT FORM OF FORMALDEHYDE?

- The DPX formation constant determined by Heck et al. (1988) was in aqueous solution and is based on the ***total*** concentration of added formaldehyde
- > 99.9% of HCHO in aqueous solution is in the form of methanediol: $CH_2(OH)_2$
- Since the rate of DPX formation is proportional to the ***total*** [HCHO], it must either reflect methanediol as the reactant or that the rate of dehydration is not rate limiting
- Either way, it relates the formation of DPX to the total amount of formaldehyde available to react with DNA
- Hence the observed ^{14}C-DPX data can tell us the *average* tissue concentration of "available" HCHO from exogenous exposure that can react with DNA
- The calibrated Conolly et al. (2001) model (or other calibrated models) can then be used to interpolate between DPX observations to determine tissue levels for other exposure concentrations

COMPARING ENDOGENOUS AND EXOGENOUS FORMALDEHYDE

- The data from Dr. Swenberg's lab for N^2-hydroxymethyl-deoxyguanine (dG) presumably also indicate the relative levels of formaldehyde "available" to react with DNA
- For the data I analyzed, I had to effectively extrapolate from 6-h exogenous dG data to compare to "continuous exposure" endogenous dG data
- This extrapolation indicates that the level of ***endogenous*** dG adducts are equivalent to an exogenous exposure of 1-2 ppm
- From the Conolly et al. (2000)/Heck et al. (1988) calibration parameters, the corresponding average tissue concentration of "available" endogenous formaldehyde is ~ 10 µM
- This suggests that, if all of the reported / measured tissue HCHO (~ 400 µM) or blood HCHO (~ 83 µM) where as "available" as exogenously delivered HCHO, the endogenous dG adduct levels would be much higher than observed

KEY POINTS

- This analysis effectively assumes that methanediol is part of the pool "available" to damage DNA and react with other cellular components – cause toxicity and/or cancer
- The analysis assumes that the relative exogenous/endogenous levels of dG adducts from Dr. Swenberg's lab reflect the relative dosimetry…
- But we also need to account for the fact that exogenous exposures which generate those levels are not 24/7
- Doing so, it appears that a large fraction of "measurable" endogenous HCHO is ***NOT*** "available" to react with DNA
- But there ***IS*** a fraction of endogenous HCHO which is "available" and biologically indistinguishable from exogenous HCHO